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RESPONSE UNDER 37 C.F.R. §1.116
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Art Unit: 1652
FRIDKIN et al	Examiner: R. Hutson
Appln. No. 09/117,380	Washington, D.C.
Filed: January 27, 1999	July 27, 2001
For: ANTI-INFLAMMATORY PEPTIDES DERIVED FROM C-REACTIVE PROTEIN	Atty.Docket: FRIDKIN=1

RESPONSE

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

The present communication is responsive to the final official action of February 27, 2001. A petition for a two-month extension of time and payment of late fee is attached hereto. Claims 1-9, 12 and 13 presently appear in this case. No claims have been allowed. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a peptide corresponding to positions 89-96 of the human C-reactive protein (CRP) of the formula: Val_{89}-Thr-Val-Ala-Pro-Val-His-Ile_{96} and modifications thereof obtained by substitution, elongation and amidation of the C-terminal or acylation of the N-terminal. These peptides may be used to inhibit the enzymatic activity of human

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Leukocyte Elastase (hLE) and/or of human Leukocyte Cathepsin G (hCG) and can be used for the treatment of chronic inflammation conditions such as rheumatoid arthritis, pulmonary emphysema and cystic fibrosis.

Claims 1, 2-9, 12 and 13 have been rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was made, had possession of the claimed invention. The examiner states that the language "but not including the entire CRP" which was added to claim 1(ix) is not supported by the specification and is thus considered new matter. This rejection is respectfully traversed.

There are two reasons why this rejection is inappropriate. First, this claim limitation is implicitly supported in the originally filed disclosure. The written description guidelines set forth at 66 FR 1099 (2001) state at 1107 that the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. The examiner has not provided any such explanation, but merely concludes that the language "is not supported by the specification". The guidelines state in the first column of 1105:

> While there is no *in haec verba* requirement, newly added claim limitations must be

> supported in the specification through express, implicit, or inherent disclosure.

That the generic disclosure of the present specification was never intended to include the entire CRP sequence is evident and at least implicit from the specification as a whole. In the first paragraph of the summary of the invention, it is stated that the present invention relates to "synthetic CRP-derived peptides ...". Furthermore, the first paragraph of the detailed description of the invention, beginning at page 4, states:

> The present invention provides a series of synthetic peptides derived from the sequence of CRP ... .

Thus, it is clear that the sequences are derived from CRP. A sequence which is derived from another sequence does not include that other sequence in its entirety. Furthermore, the background of the specification makes clear that CRP *per se* was well known in the prior art. Reference is made to footnote 63 of the Written Description Guidelines which states:

> When an explicit limitation in a claim is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation. *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998).

Those of ordinary skill in the art would have understood at the time the present application was filed that the claims to novel peptides were never intended to encompass the prior art CRP.

Indeed, for the reasons discussed below, those skilled in the art as of the filing date of the present application knew CRP did not have the ability to inhibit hLE and would have expected that CRP would also lack the ability to inhibit hCG. Thus, a person skilled in the art would have recognized that the present inventors had possession of the presently claimed invention which excludes the entire CRP.

The second reason why this rejection must be withdrawn, is that even if the genus of peptides which the inventors considered to be their invention at the time the invention was filed is considered to include CRP, as CRP is a species specifically disclosed in the specification, the recitation of the genus minus the single species fully complies with the written description requirement of 35 USC 112. The case of In re Johnson 194 USPQ 187, 196 (1977) is directly in point where it states:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirement of 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is that appellants narrowed their claims to avoid having them read on a lost interference count.

All that happened here is that applicants narrowed their claims to avoid having them read on the prior art.

Accordingly, by either interpretation of the present specification, the present language of claim 1, which specifically excludes the entire CRP sequence, complies with the written description requirement of 35 USC 112. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1 and 2 have been rejected under 35 USC 102(b) as being anticipated by Yavin. The examiner maintains this rejection on the basis that Yavin teaches the isolation of peptide fragments generated from CRP by lysosomal enzyme digestion and Yavin was in possession of additional fragments of CRP besides those identified in Table 1 that meet the limitation of claim 1(ix). The examiner recognizes that Yavin does not teach the identification of those fragments which meet the above limitation. However, the examiner believes that such a fragment exists in the RP-HPLC profile in Figure 1(a) based on the fact that not all of the CRP peptide will be "completely" digested, and there exist many fragments that are a result of "incomplete" digestion and each of these "fractions" are considered to be isolated. The examiner states that HPLC fractionation clearly constitutes isolation. This rejection is respectfully traversed.

It is apparently the examiner's position that the undefined HPLC fractions would be expected to contain undefined partial digestion fragments which will inherently include fragments within the scope of claim 1(ix). However, inherency cannot be established by probabilities or possibilities.

Reference is made to MPEP §2112 under the heading "EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY" which states:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. ...
>
> To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, ... 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (Citations omitted) ...
>
> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flow from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) ... . [Emphasis original]

See also Ethyl Molded Products Co. v. Betts Package Inc., 9 USPQ2d 1001, 1032-33 (ED Ky 1988), where it states:

> [The doctrine of necessary inherency] holds that anticipation may be established when the single prior art reference fails to disclose the claimed invention *ipsissimis verbis*, but the natural and invariable practice of the reference would necessarily

> and inherently meet all the elements of the [claimed invention]. ...
>
> ... The doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation. Probabilities are not sufficient. ... A prior inherent event cannot be established based upon speculation, or where a doubt exists.

Furthermore, the doctrine of accidental anticipation is also relevant stating that prior art is not anticipatory if the results are unappreciated and unrecognized. Note, for example, United States v. Pfizer Inc., 210 USPQ 673, 679 (ED Pa 1980), *aff'd* 216 USPQ 1016 (3rd Cir. 1982), where it states:

> Co-production of small amounts of tetracycline in the prior art which was unrecognized at the time of the Conover invention could not act as a bar to a patent on tetracycline.

The peaks in the RP-HPLC of Yavin were collected manually. Many of these peaks have very high shoulders. There is no expectation, and clearly no certainty, that each of the fractions collected by Yavin contains only a single fragment. Indeed, it would be expected that in most if not all of these fractions, multiple fragments were present. A fraction with multiple fragments is not an isolated peptide. Furthermore, the product of "incomplete" digestion does not even necessarily come out in any of the fractions. Such large fragments may come out in the first seven minutes, before which any fractions were

collected, or after 70 minutes. Note that the fragments isolated from fractions 2 and 36 are both very small peptides. It would not be expected that relatively huge partial digests would elute between these two.

The bottom line is that the examiner cannot state with certainty that any of the fractions collected by Yavin must inherently contain a single isolated peptide fragment having a sequence as required by claim 1(ix). That it may be possible is insufficient. Even probabilities are insufficient. There can be no certainty that this happens every time. As there is no such certainty, there can be no anticipation on this ground.

In addition, the present specification states, and cites art to the effect, that CRP as a whole protein has no inhibitory effect on hLE. This is not surprising as the peptides of the present invention were previously concealed within the inner hydrophobic region of each CRP subunit (page 3, lines 13-17, of the present specification). From the known three-dimensional structure of CRP, it is evident that the amino acid stretch of CRP 89-96 is concealed within the annular center of CRP's pentameric structure (Yavin, E.J., Yan, L., Desiderio, D.M., Pontet, M. & Fridkin, M., "Inhibition of human leukocyte elastase and cathepsin G by extended human C-reactive protein derived peptides and CRP-subunits". Letters in Peptide Science, 4(3):157-166 (1997) (a copy of the abstract of which is attached hereto). The steric hindrance of the intact CRP molecule does not allow binding between the amino acid stretch of CRP 89-96 (in the intact pentamer) and hLE, and in a similar fashion precludes the

possibility of binding between the amino acid stretch of CRP 89-96 (in the intact pentamer) and hCG. Thus it is reasonable to conclude, based on structural considerations, that the intact CRP molecule will have no inhibitory affect on hCG. Once the pentameric structure of CRP is disrupted into monomers, inhibition of both hLE and hCG is possible since the amino acid stretch of CRP 89-96 is exposed. In view of these structural considerations, one of ordinary skill in the art would not even expect that every partial digest of CRP which has large units including CRP-89-96 would have the required claim property of inhibiting hLE and/or hCG. This is a further reason why there is no "certainty" that a fragment within the scope of claim 1 must exist isolated in a fraction of Yavin and will always and reproducibly appear isolated in a single such fraction.

Even if it did exist in one of the fractions, this would have been totally unappreciated by Yavin and, therefore, would be considered an accidental and unintended achievement of a product which does not constitute an anticipation. Yavin was looking for capacity to modulate superoxide ion production by activated human neutrophils. This is not a property being sough by the present inventors nor is there any reason to believe that the same fragments will have the same properties. Nevertheless, it is unnecessary to rely on the doctrine of accidental anticipation in view of the fact that the examiner has not established inherent anticipation in view of the fact that there is no certainty that any of the fractions of Yavin contains an isolated peptide within

the scope of the present claims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1 and 2 have been rejected under 35 USC 102(b) as being anticipated by Shepard. The examiner states that applicant's arguments about Shepard have been found non-persuasive for the same reasons as stated with respect to the Yavin rejection. This rejection is respectfully traversed.

This rejection must fall for the same reasons as discussed above with respect to Yavin. There is no certainty that a fragment within the scope of the present invention appears in any of the fractions of Shepard. Indeed, each fraction of Shepard appears to encompass many peaks and, therefore, it is clear that the contents of each fraction are not isolated fragments. As with Yavin, anticipation cannot be based on possibilities or probabilities. Large, partially digested fragments would be expected to come out of the column either before or after the very small fragments of the various peaks. Accordingly, reconsideration and withdrawal of this rejection for the same reasons as discussed above with respect to Yavin are respectfully urged.

Claims 9, 12 and 13 have been rejected under 35 USC 103(a) as being unpatentable over Yavin, and claims 9, 12 and 13 have also been rejected under 35 USC 103(a) as being unpatentable over Shepard. The examiner states that one of ordinary skill in the art would have been motivated to create a pharmaceutical composition comprising a CRP derived peptide as taught by Yavin and to use such a pharmaceutical as an antiinflammatory medication

and a means of modulating pro-inflammatory functions of neutrophils. This rejection is respectfully traversed.

The anticipation rejection is based on an anticipation by inherency. Certainly no one of ordinary skill in the art reading Yavin and Shepard would believe that any unidentified and undetermined fragment which may exist in some fraction, would have any particular properties, particularly properties which are substantially different from the properties being sought in Yavin and Shepard. There is no suggestion that every possible fragment found by Shepard is a potent modulator of pro-inflammatory functions of human neutrophils. Only those fractions which test positive in the functionality test were considered to have any utility. Many of the fractions tested negative. Why would it be obvious that the fragments that inhibit the enzymatic activity of hLE and/or hCG are necessarily the same fragments that modulate superoxide ion production and chemotaxis. Thus, claims 9, 12 and 13 are not only allowable for the same reasons as discussed above with respect to claims 1 and 2 from which they depend, but are also allowable in their own right because it would not have been obvious to put the unidentified fragments of Yavin and Shepard into a pharmaceutical composition or to use them for any purpose. Reconsideration and withdrawal of these rejections are also respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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